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DERNS.

ANIMAL FEEDS CONTG. ~~SALISYL~~-PHENYL-ALKYLAMINELT
FOR INCREASING GROWTH PROMOTION AND REDUCING
FAT DEPOSITION

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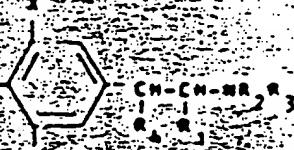
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⑮ Method of making animal feed; preparations for promoting growth and reducing fat containing phenylethanolamine derivatives; phenylethanol amine derivatives.

⑯ A method for the preparation of an animal feed composition comprising admixing an animal feed with from 0.01 to 400 grams per ton of feed of a compound of the following formula:



wherein X, Y, Z, R₁, R₂, and R₃ are as defined in the text.
Some new compounds with the same general formulae are claimed. These phenylethanol amine derivatives and their acid addition salts act as growth promoters and fat reducing agents in farm and companion animals.

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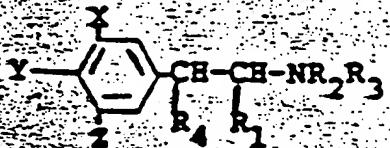
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PHENYLETHANOLAMINE DERIVATIVES AND ACID ADDITION SALTS
THEREOF USEFUL AS GROWTH PROMOTERS AND REDUCTION OF
FAT IN FARM AND COMPANION ANIMALS

Substitution products of certain 1-(aminodihalo-phenyl)-2-aminoethanes and the acid addition salts thereof are disclosed in United States Patent 3,536,712, issued on October 27, 1970. Specifically, patentees disclose methods 5 for the synthesis of said compounds and state that said compounds are useful for enhancing the blood circulation, and as bronchodilators, analgesics, sedatives, antipyretics, antiphlogistics and antitussives in warm-blooded animals. Patentees, however, exemplify only the analgesic utility. 10 They do not indicate or suggest that said compounds are useful for lowering the deposition of fat or increasing the growth rate in warm-blooded animals, particularly farm and domestic animals, such as swine, poultry, dogs, sheep, goats, cats or cattle.

15 It has now been found that the growth rate and the depression of fat deposition of meat-producing animals such as swine, chickens, turkeys, domestic pets, rabbits, sheep, goats and cattle, including calves, can be increased and the efficiency of feed utilization thereby measurably 20 improved by the oral or parenteral administration to said animals of an effective amount of a compound having the structure:



25 wherein X is hydrogen or halogen (fluorine, chlorine, iodine or bromine, but preferably chlorine or bromine; Y is hydrogen, NH₂ or NHCOR₃; Z is H, halogen (fluorine, chlorine, iodine

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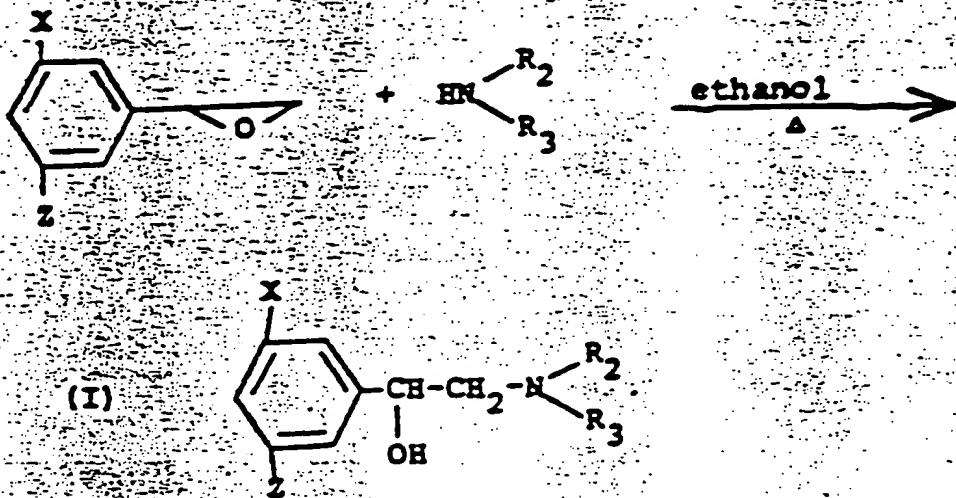
or bromine, but preferably chlorine or bromine) or OR₂; R₁ is hydrogen or C₁-C₄ alkyl; R₂ is hydrogen, C₁-C₄ alkyl (straight or branched-chain) or C₂-C₄ alkenyl; R₃ is hydrogen, C₁-C₆ alkyl (straight or branched-chain), C₃-C₆ cycloalkyl, methoxypropyl, C₂-C₅ alkenyl, phenyl, 2-hydroxyethyl, a,a-dimethylphenethyl or benzyl; and when R₂ and R₃ are taken together with the nitrogen to which they are attached, they may represent morpholino or N'-C₁-C₄ alkyl-piperazino; R₄ is hydrogen, hydroxyl or OR₆; R₅ is hydrogen or C₁-C₄ alkyl; R₆ is C₁-C₆ alkyl; with the provisos that when R₃ is phenyl, 2-hydroxyethyl, a,a-dimethylphenethyl, cycloalkyl C₃-C₆, benzyl or methoxypropyl, R₂ is hydrogen; and when Z is OH, X and Y are hydrogen; and when Y is NHCOR₅, at least one of X and Z is hydrogen; and provided also that at least one of X, Y and Z represents a substituent other than hydrogen; racemic mixtures of the above-identified compounds and the optically active isomers and non-toxic, pharmacologically acceptable acid addition salts thereof.

Preferred compounds for use in the method of this invention have the above structure wherein X and Z are each chlorine or bromine; Y is hydrogen or NH₂; R₁ is hydrogen or C₁-C₄ alkyl; R₄ is hydroxyl; or a non-toxic, pharmacologically acceptable acid addition salt thereof.

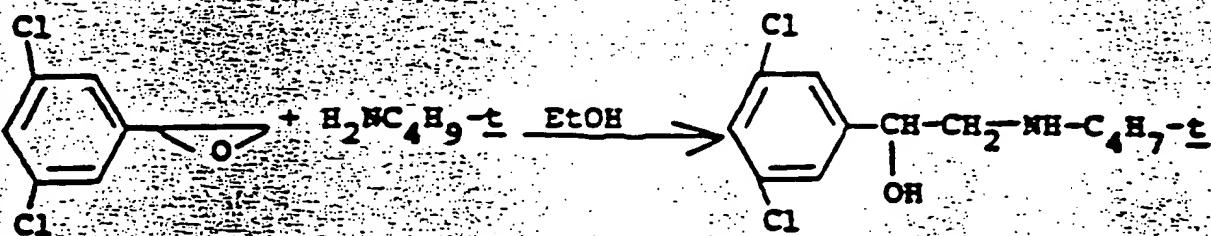
The most preferred compounds for use in enhancing the growth rate of meat-producing animals and for improving the efficiency of feed utilization thereby are: 4-amino-a-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride; 4-amino-3,5-dibromo-a-[(diisopropylamino)methyl]-benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-a-[(diisopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dibromo-a-[(tert-butylamino)methyl]-benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-a-[(methylamino)methyl]-benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-a-[(allylamino)methyl]benzyl alcohol; 4-amino-3-bromo-a-[(tert-butylamino)methyl]-5-chlorobenzyl alcohol hydrochloride; a-[(4-amino-3,5-dichlorophenyl)-4-morpholinethenol hydrochloride; 4-amino-3-bromo-a-[(tert-butylamino)methyl]-5-

chlorobenzyl alcohol, hydrochloride and α -[(tert-butylamino)-methyl]-3,5-dichlorobenzyl alcohol hydrochloride.

It is found, that formula (I) compounds below (wherein Y is hydrogen) can be prepared by the condensation of an appropriately substituted styrene oxide with the appropriately substituted amine in the presence of an inert solvent, such as a lower alcohol at or near the boiling point of same, as shown below:



20 wherein X and Z are halogen, R₂ and R₃ are as hereinabove defined and Y is hydrogen. Thus, 3,5-dichlorostyrene oxide can be reacted with an equimolar or molar excess of t-butylamine in ethanol at reflux from about 1 to about 8 hours, or until the reaction is essentially complete and the desired α -[t-butylamino)methyl]-3,5-dichlorobenzyl alcohol is obtained as illustrated below:

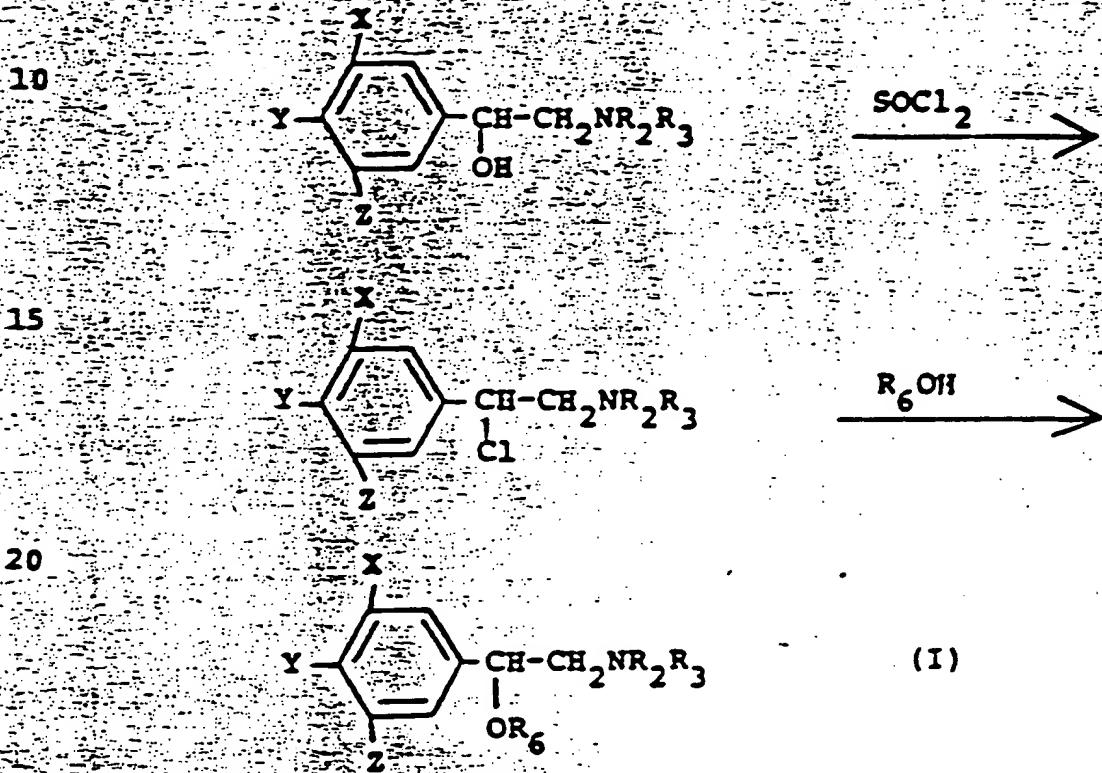


The thus obtained product can be purified by known procedures, such as chromatography or recrystallization of salt thereof.

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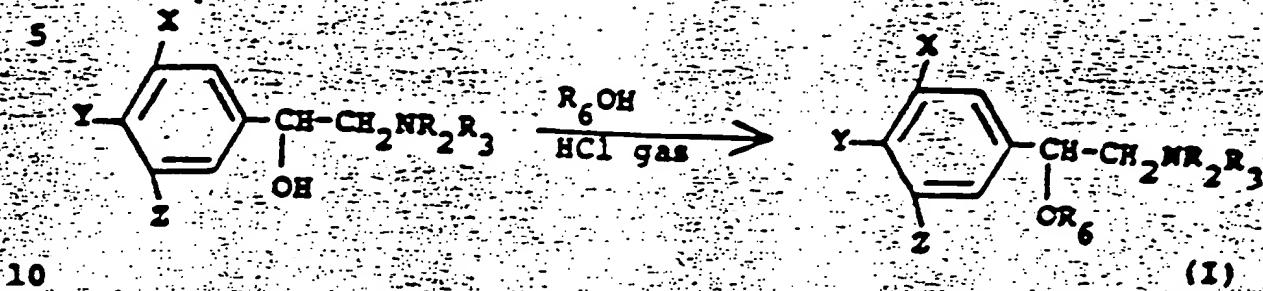
action. The thus obtained halo compound is isolated by conventional laboratory methods and is then reacted with the appropriate alcohol, under an inert blanket of gas, such as nitrogen at a temperature range of from about 0 to 5°C. Thus

5 thus obtained formula (I) product is then isolated by standard laboratory methods and purified, if so desired. The above reaction sequence may be graphically illustrated as follows:



25 wherein X, Y, Z, R₂, R₃ and R₆ are as hereinabove defined.

Alternatively, a formula (I) compound wherein R₄ is OR₆ may be prepared by dissolving the corresponding formula (I) compound wherein R₄ is OH in the corresponding R₆OH alcohol and saturating the thus obtained solution 30 with dry HCl gas. The reaction mixture is then stirred at room temperature for a period of time sufficient to essentially complete the reaction and the product is then isolated by standard laboratory procedures and purified, if so desired. This reaction sequence may be illustrated as 35 follows:



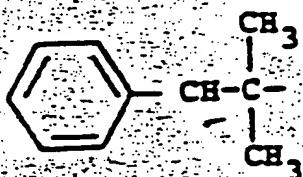
15 wherein X, Y, Z, R₂, R₃ and R₆ are as hereinabove defined.

In the present specification and claims the term *a,a-dimethylphenethyl* means a structure having the following configuration:

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When orally administered in the feed, generally about 0.01 to 300 grams per ton of feed of the above-identified phenylethanolamine derivative or acid addition salt thereof, is effective for enhancing the growth rate and improving the efficiency of feed utilization by the above-mentioned meat-producing animals.

Since the effective and preferred dietary levels of the active ingredient vary somewhat from species to species in the above-mentioned animals said levels for each animal species are listed in Table I below on a gram per ton of feed basis:

Table I

Compound	Effective Feed Level g/ton	Preferred Level g/ton	Animal
10 Formula (I)	0.1-300	1-200	Swine
	0.1-200	1-100	Sheep, Goats
	0.01-50	0.1-10	Chickens, Rabbits
	0.01-50	0.1-10	Turkeys
	0.1-200	1-100	Cattle

15 Animal feed compositions which will provide the desired growth promotion and feed efficiency in the above-mentioned animals can be prepared by admixing the phenylethanolamine derivative or acid addition salt thereof, or an animal feed supplement containing said compound, with a sufficient quantity of an appropriate animal feed to provide the desired level of active compound in said feed.

20 Animal feed supplements can be prepared by admixing about 75% to 95% by weight of the phenylethanolamine derivative or acid addition salt thereof, with about 5% to 25% by weight of a suitable carrier or diluent. Carriers suitable for use to make up the feed supplement compositions include the following: alfalfa meal, soybean meal, cotton-seed oil meal, linseed oil meal, sodium chloride, cornmeal, cane molasses, urea, bone meal, corncob meal and the like.

25 The carrier promotes a uniform distribution of the active ingredient in the finished feed into which the supplement is blended. It thus performs an important function by ensuring proper distribution of the active ingredient throughout the feed.

30 If the supplement is used as a top dressing for feed, it likewise helps to ensure uniformity of distribution of the active material across the top of the dressed feed.

35 For parenteral administration the phenylethanol-

amine derivative may be prepared in the form of a paste or pellet and administered as an implant, usually under the skin of the head or ear of the animal in which enhanced growth rate and/or improved efficiency of feed utilization is sought.

In practice, parenteral administration generally involved injection of a sufficient amount of the above-said ethane derivative to provide the animal with from 0.001 to 100 mg/kg of body weight of the active ingredient. The preferred dosage level for swine is 0.01 to 50 mg/kg of body weight and for cattle the range of from 0.001 to 50 mg/kg of body weight of the active phenylethanolamine derivative is preferred. The preferred dose level of said ethane derivative for poultry is about 0.001 to 35 mg/kg of animal body weight and the preferred dose level of said ethanol derivative for sheep and goats is 0.001 to 40 mg/kg of animal body weight. The preferred dose level for rabbits and domestic pets is 0.001 to 35 mg/kg of animal body weight.

Paste formulations can be prepared by dispersing the active ethanol derivative in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing an effective level of the phenylethanolamine derivative can be prepared by admixing the above-said active ingredient with a diluent such as carbowax, biodegradable polymers, carnuba wax, or the like. A lubricant, such as magnesium stearate or calcium stearate may be added to improve the pelleting process if desired.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increased growth rate and/or improved efficiency of feed utilization by said animal. Moreover, it has been found that additional implants may also be introduced periodically during the treatment period in order to maintain the proper drug release rate in the animal's body.

In addition to enhanced growth promotion and improved efficiency of feed utilization by meat-producing animals, the compounds of the present invention have the addi-

ed advantage that, at selected levels of administration they depress the deposition of fat in said animals. This biological response has substantial advantage to poultrymen and swine producers since administration of said compounds at selected levels yields leaner animals which command premium prices from the meat industry.

The invention has several advantages for the pet owner or veterinarian who wishes to trim unwanted fat from pet animals. For poultry men and swine raisers, using the method of the present invention were attained increased yields of leaner animals which command higher prices from the meat industry. Surprisingly, it is also noted that feed efficiency and animal growth rate are significantly enhanced when the compounds of the present invention are administered to swine and poultry at selected dose levels.

The following examples illustrate the invention.

Example 1

Evaluation of test compounds as animal growth promoters

CPI female mice from Carworth Farms are received when they are six weeks old. They are housed ten to a cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow (see description below), which is supplied ad libitum. Water is also allowed ad libitum.

Thirteen days after arrival, the mice are weighed in groups of ten and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following tables. Twelve days later the mice are weighed again and the experiment terminated. Test data are provided in Table II below wherein data are reported as percentage gain over controls. The following is a description of the diet to which the growth-promoting compounds were added.

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DIET

Guaranteed Analysis

Crude protein not less than 23.08 ..

Crude fat not less than 4.58 493
1613

75230

975980

Crude fiber not more than 6.0%

Ash not more than 9.0%

Ingredients

Meat and bone meal, dried skimmed milk, wheat germ meal,
5 fish meal, animal liver meal, dried beet pulp, ground ex-
truded corn, ground oat groates, soybean meal, dehydrated
alfalfa meal, cane molasses, animal fat preserved with BHA,
vitamin B₁₂ supplement, calcium pantothenate, choline
chloride, folic acid, riboflavin supplement, brewer's dried
10 yeast, thiamin, niacin, vitamin A supplement, D-activated
plant sterol, vitamin E supplement, calcium carbonate, di-
calcium phosphate, iodized salt, ferrec ammonium citrate,
iron oxide, manganous oxide, cobalt carbonate, copper oxide,
zinc oxide.

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TABLE II

Evaluation of Test Compounds as Animal Growth Promoters

Dose	Initial Mouse Wt. (g)	Final Mouse Wt. (g)	Gain over Control	Gain over Control	
				0	5
4-Amino- <i>a</i> -(<i>tert</i> -butyl)- aminoethyl)-3,5-dichlorobenzyli alcohol hydrochloride					
(ppm in diet)					
	23.46	24.67	1.21		
	23.46	24.49	1.03		
	22.79	24.62	1.83		
	24.10	25.98	1.88		
	24.23	25.52	1.29		
	23.63	24.93	1.30		
	23.33	24.76	1.43		
	22.75	23.86	1.11		
Control Average	23.47	24.05	1.39	6.7	
					5.92

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TABLE II (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Doseage	Initial Wt. (g)	Final Wt. (g)	Gain Over Control	Gain (grams)	
				Initial Mouse Wt. (g)	Final Mouse Wt. (g)
50	22.95	25.63	2.68		
	23.91	26.14	2.23		
	24.26	26.30	2.04		
	23.71	26.02	2.32		
			66.9		
100	23.50	25.39	1.89		
	23.80	26.04	2.24		
	23.00	25.65	2.65		
	23.43	25.69	2.26		
			62.6		
200	23.03	24.80	1.77		
	24.50	26.12	1.62		
	23.06	25.04	1.96		
	23.54	25.32	1.78	7.6%	20.1
					1.56%

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The procedure described above is repeated using control animals for each test. Twelve days after the tests are started the animals are weighed and the test terminated. The results of each test are reported in Table III below as weight gains for each test group and percent gain for each group over controls.

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TABLE III

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Control
4-Amino-3,5-dibromo-a-[(tert-butylamino)methyl]benzyl alcohol hydrochloride	400	16.5	+22.2
	200	20.4	+51.1
	100	22.9	+69.0
	50	23.3	+72.6
4-Amino-3,5-dibromo-a-[(diisopropylamino)methyl]benzyl alcohol hydrochloride	200	20.2	+16.4
	100	16.9	+22.5
P-amino-a-[(dimethylamino)methyl]benzyl alcohol	200	17.6	+28.3
	100	15.6	+13.0
P-amino-a-[(diisopropylamino)methyl]benzyl alcohol hydrochloride	200	16.5	+18.7
	100	14.2	+2.2
4-Amino-3,5-dichloro-a-[(dimethylamino)methyl]benzyl alcohol hydrochloride	100	10.4	+7.6
4-Amino-3,5-dichloro-a-[(diisopropylamino)methyl]benzyl alcohol hydrochloride	200	23.9	+66.0
	100	21.3	+47.9

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TABLE III (Continued)

Evaluation of Test Compounds as Antial Growth Promoters

Compound	Dosage (ppm)	Gain over Control (grams)	Gain over Control (%)
4-Amino-3,5-dichloro- α -[(oxylohexylamino)methyl]benzyl alcohol hydrochloride	200	19.3	+48.5
	100	16.3	+25.4
P-Amino- α -[(tert-butylamino)methyl]benzyl alcohol	200	19.6	+88.5
	100	18.2	+75.0
	50	17.9	+72.1
	25	13.6	+30.8
P-Amino- α -[(methylamino)methyl]benzyl alcohol hydrochloride	200	15.6	+54.5
	100	18.9	+87.1
P-Amino- α -[(ethoxyamino)methyl]benzyl alcohol hydrochloride	100	14.8	+18.4
α -(4-Amino-3,5-dichlorophenyl)-4-morpholineethanol hydrochloride	200	15.9	+34.7
	100	14.0	+18.6
4-Amino- α -[(eg-butylamino)methyl]-3,5-dichlorobenzy alcohol	200	13.2	+16.8

TABLE III (Continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain Over Control
4-Amino-3,5-dichloro-a-[(-3-methoxypropyl)amino]-methyl benzyl alcohol	200 100	15.1 23.0
4-Amino-3,5-dichloro-a-[(benzylamino)methyl]benzyl alcohol hydrochloride	200 100	17.4 18.1
4-Amino-3,5-dichloro-a-[(butylamino)methyl]-3,5-dichlorobenzylic alcohol	100	14.6
4-Amino-3,5-dichloro-a-[(isopropylamino)methyl]-3,5-dichlorobenzylic alcohol	200 100	19.1 23.2
4-Amino-3,5-dichloro-a-[(4-methyl-1-piperazinyl)-methyl]benzyl alcohol	200 100	9.1 9.3
4-Amino-3,5-dichloro-a-[(4-methyl-1-piperazinyl)-methyl]benzyl alcohol	200 100	13.1 10.9

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TABLE III (Continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (mg)	Gain Over Control
4-Amino- α -(anilinoethyl)-3,5-dichlorobenzyl alcohol hydrochloride	100	+13.4 +19.0
4-Amino-3,5-dichloro- α -(hexylamino)methylbenzyl alcohol	200	+16.8 +15.9
4-[tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride	200	+19.3 +33.1
4-Amino-3,5-dichloro- α -(diethylamino)methylbenzyl alcohol hydrochloride	100	+20.2 +39.3
4-[mallylamino)methyl]-4-amino-3,5-dichlorobenzyl alcohol	100	+17.5 +20.7
4-Amino- α -(anilinoethyl)-3,5-dichlorobenzyl alcohol	200	+16.0 +118.2
4-Amino- α -(anilinoethyl)-3,5-dichlorobenzyl alcohol	100	+17.1 +122.1

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TABLE III (Continued)
Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dose (ppm)	Gain Over Control	
		Gain (grams)	% Gain Over Control
4-Amino-3-bromo- α -[(tert-butyloxino)methyl]-3,5-dichloro-benzyl alcohol hydrochloride	200	22.7	+37.6
	100	23.8	+44.5
4-Amino-3-bromo- α -[(tert-butyloxino)methyl]-3,5-dichloro-benzyl alcohol	200	18.5	+69.6
	100	19.5	+69.6
α -[(tert-butyloxino)methyl]- β -hydroxybenzyl alcohol hydrochloride	200	15.0	+9.0
	100	19.9	+37.2
α -[(isopropylamino)methyl]- β -hydroxybenzyl alcohol	400	-	+51.4
	200	-	+53.0
	100	-	+39.7
α -[(Amino)ethyl]- β -hydroxybenzyl alcohol hydrochloride	200	-	+1.1
	100	-	+30.1
4-Amino-N-tert-butyl-3,5-dichloro- β -methoxyphenethyl hydrochloride	200	16.8	+31.2
	50	21.6	+31.1

Example 2

Evaluation of test compounds as animal growth promoters

The procedure of Example 1 is used in this evaluation. The diet is the same as described in said example 5 and data obtained are reported as percent gain over controls. Data are reported in Table IV below.

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Evaluation of Test Compounds as Animal Growth Promoters

TABLE IV.

<u>Dosage</u>	<u>Initial Wt. (g)</u>	<u>Final Wt. (g)</u>	<u>Gain (grams)</u>	<u>Gain Over Control</u>
0	24.49	25.17	.68	
	24.25	26.06	1.81	
	23.65	25.43	1.78	
	22.83	24.33	1.50	
	24.39	25.59	1.20	
	24.36	26.06	1.70	
	23.11	24.50	1.39	
	23.54	24.82	1.28	
<u>Average</u>	<u>23.83</u>	<u>25.25</u>	<u>1.42</u>	<u>-</u>

TABLE IV (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Dose/kg	Initial Wt. (kg)	Final Wt. (kg)	Gain (grams)	Gain Over Control	
				Test	Control
200					
23.46	23.49	2.03			
23.68	25.97	2.37			
23.56	25.40	1.84			
Average	23.57	25.62	2.05	111.1	

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Iodine	0.35	1.75
Cobalt	0.25	1.25
Calcium minimum	15.30	
Calcium maximum	17.35	

**Vitamin Premix for 1-ton

	Weight in Gram
DL Methionine	433.8
BHT (butylated hydroxy toluene)	113.5
Vitamin A (30,000 mcg/g)	108.0
Vitamin D ₃ (200,000 mcg/g)	5.0
Vitamin E (20,000 mcg/lb)	48.4
Riboflavin	4.0
Niacinamide	23.0

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TABLE V

Mean Weight Gain and Feed Efficiency of Control and Test Compound - Treated Chicks

Thirteen-Day Battery Testing

Treatment	Control			1/4 over Control			1/2 over Control			1/4 over Control		
	Mean In Diet	Oz/tin (g)	Control	Mean In Diet	Oz/tin (g)	Control	Mean In Diet	Oz/tin (g)	Control	Mean In Diet	Oz/tin (g)	Control
Control	0	266.5	-	-	-	-	1.40	-	-	1.40	-	-
1- <i>alpha</i> - <i>alpha</i> -(1- <i>tert</i> -butylamino)ethyl-3,5-dichlorofentanyl hydrochloride	0.3	271.0	-	2.0	1.40	0	0	-	-	1.40	0	-
1- <i>alpha</i> - <i>alpha</i> -(1- <i>tert</i> -butylamino)ethyl-3,5-dibromo-3-(1- <i>tert</i> -butyl)-1-methoxyethyl hydrochloride	0.6	271.3	-	2.9	1.39	0.1	0	-	-	1.39	0.1	-
1.25	259.9	-	-	2.5	1.41	0.7	0	-	-	1.39	0.7	-
2.5	260.8	-	-	2.1	1.39	0.7	0	-	-	1.39	0.7	-
5.0	251.9	-	-	5.5	1.40	0	0	-	-	1.39	0.7	-
5.0	270.3	-	-	1.1	1.37	0.7	0	-	-	1.37	0.7	-
5.0	265.2	-	-	0.5	1.36	0.7	0	-	-	1.36	0.7	-
5.0	267.5	-	-	0.5	1.36	0.7	0	-	-	1.36	0.7	-
5.0	270.6	-	-	1.6	1.40	0	0	-	-	1.40	0	-
0.3	270.6	-	-	2.0	1.39	0.7	0	-	-	1.39	0.7	-
0.6	271.6	-	-	2.0	1.39	0.7	0	-	-	1.39	0.7	-
1.25	267.5	-	-	0.5	1.36	0.7	0	-	-	1.36	0.7	-
2.5	265.2	-	-	0.5	1.36	0.7	0	-	-	1.36	0.7	-
5.0	270.3	-	-	1.1	1.37	0.7	0	-	-	1.37	0.7	-

Example 4Evaluation of test compounds as antilipogenic agents -Mouse tests

CPI female mice from Carworth Farms are received 5 when they are six weeks old. They are housed ten to a cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow (see description below), which is supplied ad libitum.

10 The following is a description of the diet to which the growth-promoting compounds were added.

DIETGuaranteed Analysis

15	Crude protein not less than	23.0%
	Crude fat not less than	4.5%
	Crude fiber not more than	6.0%
	Ash not more than	9.0%

Ingredients

Meat and bone meal, dried skinned milk, wheat germ meal, 20 fish meal, animal liver meal, dried beet pulp, ground extruded corn, ground oat groats, soybean meal, dehydrated alfalfa meal, cane molasses, animal fat preserved with BHA, vitamin B₁₂ supplement, calcium pantothenate, choline chloride, folic acid, riboflavin supplement, brewer's dried 25 yeast, thiamin, niacin, vitamin A supplement, D-activated plant sterol, vitamin E supplement, calcium carbonate, di-calcium phosphate, iodized salt, ferric ammonium citrate, iron oxide, manganese oxide, cobalt carbonate, copper oxide, zinc oxide. Water is also allowed ad libitum.

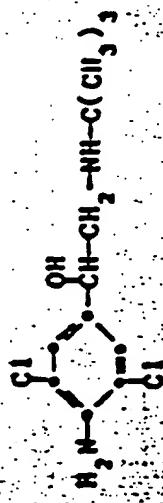
30 Thirteen days after arrival, the mice are weighed in groups of ten and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following tables. Twelve days later the mice are weighed again the experiment terminated. At least three cages (30 mice) of untreated controls are included in each test. Test data are provided in Table VI below wherein data are reported as percent body fat, percent change in body fat from controls and gain per mouse.

in grams.

TABLE V

Antilipogenic Agent Evaluation and Growth Enhancement Evaluation in Hogs

Compound	Level in Diet (ppm)	Number of Hogs per Treatment	Average Initial Weight (kg)	Average Final Weight (kg)	Gain per Hog (kg)	Change in %	Body Fat Frog (kg)	Control Fat
			(A)	(B)	(B) - (A)	(B) - (A) %		
	0	50	23.6	25.0	1.4	11.95		
	50	30	23.7	26.0	2.3	11.95		
	100	30	23.4	25.7	2.3	10.23	-11.80	
	200	30	23.5	25.3	1.8	10.50	-12.13	
	400	30	23.4	24.9	1.5	9.10	-23.80	



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TABLE VI
Antilipogenic Agent Evaluation and Growth Enhancement Evaluation in Mice

Compound	Level in Diet (ppm)	Number of Mice per Treatment	Average Initial Weight (K)	Average Final Weight (K)	Gain (K)	Change in Percent per Mouse	Body Fat from Control Fat
	0	50	23.6	25.0	1.4	11.95	-
	50	30	23.7	26.0	2.3	11.95	0
	100	30	23.4	25.7	2.3	10.23	-11.40
	200	30	23.5	25.3	1.8	10.50	-12.13
	400	30	23.4	24.9	1.4	9.10	-23.80



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Percent Body Fat Determination of Mice

A. Preparation of Carcasses:

Stomach and intestines are removed from each mouse. All other viscera, including skin and fur, remain intact.

5 Each cage of mice (10) are weighed and added to a 1000 ml beaker and autoclaved at 120°C (15 psi) for 30 minutes.

Carcasses from each cage are then blended and homogenized. The homogenate is weighed and duplicate 5-gram samples are removed for analysis.

10 B. Fat Analysis:

Fifteen milliliters (ml) of concentrated hydrochloric acid is added to each 5-gram sample and mixed well. Samples are heated in an 84°C water bath for 2 hours. To extract the fat, thirty ml of petroleum ether is added to 15 each samples, 15 ml at a time, and mixed well on a Vortex mixer. The aqueous and organic phases are separated by low speed centrifugation and the ether layer (containing fat) is extracted into tared 30 ml beakers. After evaporating to dryness the beaker containing fat is reweighed to determine grams of fat per five grams of homogenate. Total body fat in the carcass is calculated as follows:

$$\% \text{ Fat} = \frac{\left[\begin{array}{l} \text{grams fat} \\ \text{in sample} \end{array} \right] \left[\begin{array}{l} \text{grams total} \\ \text{homogenate} \end{array} \right]}{\left[\begin{array}{l} \text{gram weight} \\ \text{of sample} \end{array} \right] \left[\begin{array}{l} \text{carcass weight} \\ \text{of mice (g)} \end{array} \right]} \times 100$$

Example 5

Antilipogenic Evaluation of test compounds - Mouse Study

30 CPI female mice, 55 days old, are weighed in groups of 10 and allotted to cages to minimize weight variation among cages. Treatments are randomly assigned to cages.

Each of the treatments are tested in 3 replicates, i.e., in 3 cages of 10 mice each. There are 10 cages of 10 control mice each. Drugs are mixed in the diet at the dosage 35 level indicated. Feed and water are offered ad libitum for the 12-day test period. Feed spilled is collected during the test period. At the end of the test period, the collected feed is weighed and the mean feed consumption per cage of ten

mice is determined for each treatment. The mice are weighed as a group of 10 and the weight gain determined. The mice are sacrificed by cervical dislocation. The right uterine fat pad of each mouse is removed. The fat pads for each cage of 10 mice are weighed as a unit.

To establish correlation between the percent reduction in fat pad weights of treated animals and percent reduction in total body fat of treated animals, animals from several treatment groups are evaluated for total body fat to using the body fat determination described in Example 5. Data obtained are reported in Table VII for those groups upon which such determination has been made. From percent reduction in fat pad weight and the total fat determinations for the groups tested, it can be seen that a reduction in fat pad weights of animals is generally indicative of a reduction of total body fat of the treated animals.

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TABLE VII

Antilipogenic Evaluation of Test Compounds - House Study

Compound	Doseage (mg.)	% Reduction in Fat Pad Weight vs. Controls			Average 2 Tests
		Animal Fat	Vegetable Fat	Ve Control	
1-amino-3,5-dibromo-a-[(tert-butylamino)ethyl]benzyl alcohol hydrochloride	400	-21.4	-11.1	-9.4	-14.6
	200	-27.5	-13.9	-5.3	-18.4
	100				
1-amino-3,5-dibromo-a-[(tert-butylamino)ethyl]benzyl alcohol hydrochloride	400	-50.0	-28.1	-23.8	-41.2
	200	-37.9	-12.1	-11.5	-26.2
	100				
1-amino-3,5-dibromo-a-[(tert-butylamino)ethyl]benzyl alcohol hydrochloride	200	-14.7	-6.7	-9.9	-10.2
	100	-10.0	-4.2	-5.3	-7.6
	50	-14.4	-5.3	-6.3	-8.3
1-amino-3,5-dibromo-a-[(tert-butylamino)ethyl]benzyl alcohol hydrochloride	200	-64.7	-36.2	-36.3	-50.9
	100	-56.2	-30.2	-30.3	-48.2
	50	-50.9	-25.9	-25.9	-38.9

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TABLE VII (Continued)

Antilipogenic Evaluation of Test Compounds - Mouse Study

Compound	Dosage (ppm)	% Reduction in Fat		% Animal Fat vs. Controls
		Pad Weight	Pad Weight vs. Controls	
1- <i>benzino</i> -3,5-dichloro- <i>a</i> -[(diethylamino)methyl] benzyl alcohol hydrochloride	200	-12.0		-5.4
1- <i>benzino</i> -3,5-dichloro- <i>a</i> -(benzylamino)methyl benzyl alcohol hydrochloride	200	-27.7	-21.1	-1.7
	100			
1- <i>benzino</i> -3,5-dichloro- <i>a</i> -(butylamino)methyl benzyl alcohol	200	-21.5	-16.5	-16.7
	100			
1- <i>benzino</i> -3,5-dichloro- <i>a</i> -(isopropylamino)methyl benzyl alcohol	200	-50.2	-36.9	-25.5
	100			
1- <i>benzino</i> -3,5-dichloro- <i>a</i> -(1,1-dimethylpropylamino)methyl benzyl alcohol	200	-21.7	-24.7	-13.0
	100			
1- <i>benzino</i> -3,5-dichloro- <i>a</i> -(1,1-dimethylbutylamino)methyl benzyl alcohol	200	-19.8	-20.4	-22.5
	100			-16.8

TABLE VII (continued)

Antilipogenic Evaluation of Test Compound - Mouse Study

Compound	Doseage (ppm)	% Reduction in Fat		vs Control
		Pad Weight	Animal Fat	
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	200	-17.0	-19.8	-21.4
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	100	-18.7	-26.2	-26.6
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	100	-7.5	-12.1	-13.7
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	50	-24.5	-31.1	-34.7
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	100	-30.7	-37.4	-40.0
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	200	-6.7	-15.2	-17.6
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	200	-20.5	-27.6	-30.0
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	50	-10.3	-17.4	-19.0
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	100	-12.1	-19.7	-21.3
4-anino-3-butyl-3,5-dichlorophenethylamine hydrochloride	200	-24.8	-31.5	-34.1

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below. Results of this study are reported in Table VIII. 10 are removed before the carcasses are homogenized. 10 are described in Example 4, excepting that the skin and organs are discarded. Percent body fat is determined in the same manner for each treatment. Period is fourteen days and 10 rats, one per cage, are used. 5 are described in Example 1, excepting that the cage contains 10 rats. The proportion of test compounds as antidiopogenic agents was 100:60:60.

Antidiopogenic evaluation of test compounds - Rat study

Example 7

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TABLE VIII

Antidiuretic Evaluation of Test Compounds and Growth Rate Evaluation in Rats

Compound	Level in Diet (ppm)	Number of Rats	Average Initial Weight (g)	Average Final Weight (g)	Average Gain per Rat (g)	1 Rat in 1000 Grossed from Control	Change in Rat Weight from Control
<chem>N2Nc1cc(Cl)cc(OCCN(C)C)c(Cl)c1</chem>	0	10	72.7	149.1	76.4	4.67	-
	25	10	78.3	159.3	81.0	3.04	-31.9
	100	9	76.6	159.8	83.2	2.51	-42.0
	400	10	73.2	146.4	73.2	2.71	-45.6

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5 Four-week old female outbred rats (5-gm males) were fed each of three compounds as an equal feed add. -
 10 each used in these studies is Purina Laboratory Chow which
 contains 11% protein, 14% protein and 10% protein off. The basic
 diet used in these studies is Purina Laboratory Chow which
 is supplied as 1-lb. bags. Water is also given as 1-lb. bags.
 15 Four days after arrival, the animals are weighed
 and allotted to treatment groups to minimize weight variation. Drugs are
 administered in the feed at 2 ppm, 10 ppm and 50 ppm for a
 period of 12.5 weeks. Animals are weighed weekly and feed
 consumption corrected for spillage recorded daily. The
 results of this trial are shown below in Table IX.

EXHIBIT 8

TABLE IX

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Evaluation of Test Compounds as Animal Feed Additives for the Enhancement of Growth Rate
and Improvement in Feed Efficiency - Mice

Treatment	Dose ppm	Feed (g)	Gain ^a (g)	Consumption ^b (g)	Feed/Gain Improvement
Control		157	1304	8.31	
4-Amino- <i>a</i> -(<i>tert</i> -butylaminoethyl)-3,5-dichloro- benzyl alcohol hydrochloride	2	178 (+13.4%)	1443 (+10.7%)	8.11 (+2.4%)	-
	10	186 (+18.5%)	1467 (+11.5%)	7.89 (+5.1%)	-
	50	175 (+11.5%)	1394 (+6.9%)	7.97 (+4.1%)	-
4-Amino-3,5-dibromo- <i>a</i> -[<i>(tert</i> -butylamino)methyl]- benzyl alcohol hydrochloride	2	164 (+4.5%)	1362 (+4.5%)	8.3 (0.1%)	-
	10	185 (+7.8%)	1459 (+11.9%)	7.89 (+5.1%)	-
	50	184 (+17.2%)	1416 (+8.6%)	7.70 (+7.3%)	-

^aValues given are the total average gain (g) per rat for the entire experimental period.

^bValues given are the total average feed consumed per rat for the entire experimental period.

Figures in parentheses are % improvement over control.

30 and carefully acidified to pH 3 with concentrated HCl. The mixture is extracted with 300 ml of CH_2Cl_2 and the extract is dried over MgSO_4 , filtered, and evaporated to dryness. It reacts to afford the epoxide as a clear yellow oil.

addition is completed, the reaction mixture is stirred 16 hours at ambient temperature, which is optimum by graphical analysis of the data to be presented. The mixture is cooled to 5°C, washed 100 ml of H_2O , the aqueous mixture is cooled to 5°C, and 50 ml of CH_3CO_2H is added to precipitate the product. The precipitate is collected and washed with H_2O to remove any remaining CH_3CO_2H .

The intermediate 3',5'-dichlorostyrene oxide needed for preparing the title compound is made by reducing 28.4 g of 3',5'-dichloropropenacyl bromide in 125 ml of absolute ethyl alcohol at 5.0°C with 8 g of zinc, added portionwise. After the

15 The free base of the title compound is obtained by neutralization of the title compound with aqueous 10% NaOH. Other salts of the free base are obtained by treatment of the free base in the above-mentioned procedure (aqueous ethanol). With addition of the appropriate acids, 20 salts such as H_2SO_4 , H_3PO_4 , HNO_3 , CH_3SO_3H , toluenesulfonic acid and picric acid.

Anal. : Calcd for $C_{12}H_{17}NOCl_2HCl$: C, 48.26; H, 6.08; N, 4.06. Found: C, 48.49; H, 6.17; N, 4.66.

5 outside in 50 ml of absolute ethanol and 20 ml of *t*-butyl-
amide is beat ed gently at reflux for 8 hours and the mixture
is evaporated to dryness. The clear yellow syrup is dis-
solved in 75 ml of ethanol and 25 ml of H_2O , and the
solution is cooled to 5°C and acidified with 3N HCl . This
solution is evaporated to dryness in a vacuum and the
white solid is recrystallized from acetone to afford
10 solution is evaporated to dryness in a vacuum and the residue
which is solid is recrystallized from acetone to afford
2.81 g, m.p. 218-221°C.

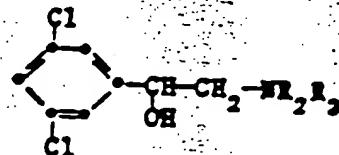
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5-(Tetra-p-tolylamino)benzyl-3,5-dichlorobenzoate AL60501

2.5 hours and cooled to room temperature. After stirring for 16 hours at room temperature, the mixture is cooled in ice for 2 hours and filtered. The filter cake is washed with 50 ml of CHCl_3 and the combined filtrates are twice decolorized with activated carbon, filtered, and evaporated to dryness in vacuo to afford the orange oil of the 3,5-dichlorostyrene oxide.

EXAMPLE 10

The following 3,5-dichlorophenyl compounds (A) related to the title compound of Example 9 are prepared by the method described in Example 6 by substituting t-butyl amine with $\text{R}_2\text{R}_3\text{NH}$ amines.



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Compound	<u>L</u>	<u>R3</u>
1	H	H
2	H	CH_3
3	H	C_2H_5
4	H	$\text{H}_3\text{C}_2\text{H}_7$
5	H	$\text{n-C}_3\text{H}_7$
6	H	$\text{n-C}_6\text{H}_{13}$
7	H	cyclohexyl
8	H	$\text{CH}_2\text{-CH=CH}_2$
9	H	$\text{CH}_2\text{-CH=CH-CH}_3$
10	H	$\text{CH}_2\text{C=CH}$

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A (Continued)

<u>Compound</u>	<u>R₂</u>	<u>R₃</u>
5	H	phenyl
12	H	methoxymethyl
13	H	benzyl
14	CH ₃	CH ₃
15	C ₂ H ₅	C ₂ H ₅
10	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂
16	—C ₃ H ₇	—C ₃ H ₇
17	CH ₂ —CH=CH ₂	—CH ₂ —CH=CH ₂
18	H	cyclopropyl
19	—CH ₂ —CH ₂ —O—CH ₂ —CH ₂ —	
20	H	n-butyl
21		
22	H	C(CH ₃) ₂ —CH ₂ — 

EXAMPLE 11

a-[(Tert-butylamino)methyl]-3,5-dibromobenzyl Alcohol Hydrochloride

This title compound is prepared from 3,5-dibromo-styrene oxide in the same manner as described in Example 9. The starting materials for this styrene oxide are similarly prepared starting with 3',5'-dibromoacetophenone.

25 The corresponding a-[(isopropylamino)methyl]-3,5-dibromobenzyl alcohol hydrochloride is prepared by substituting isopropyl amine for t-butyl amine.

EXAMPLE 12

 α -Hydroxy-a-[(isopropylamino)methyl]benzyl Alcohol Hydrochloride

In 135 ml of 95% ethanol, 36.75 g of α -hydroxyacetophenone, 36.5 g of benzyl chloride, 1.75 g of XI, and 24.6 g of K₂CO₃ are stirred and heated at reflux for 5 hours. The mixture is cooled, evaporated in vacuo to remove ethanol and 35 100 ml of H₂O is added. The mixture is then extracted with diethyl ether three times to afford 350 ml of extract, which is further washed with 50 ml of H₂O, saturated NaHCO₃ solu-

tion (2 x 30 ml), 50 ml of H_2O , and 50 ml of brine in succession. The filtrate is dried over Na_2SO_4 and evaporated to dryness. The residual oil is distilled to afford 49.13 g of m -benzylxyacetophenone, b.p. 145-147°C/0.2 mm. Bromination of 186 g of this acetophenone is accomplished with 349 g of $CuBr_2$ in 1 l of $CHCl_3$ /1.5 l of ethanol heated at reflux. A N_2 sweep is used to remove HBr generated. After 4 hours, the mixture is filtered and the filter cake is washed with $CHCl_3$ (2 x 100 ml). The filtrate is evaporated in vacuo to afford an oil, which is dissolved in 200 ml of absolute ethanol (2 x 50 ml), and dried to afford 64.28 g m -benzylxyphenacyl bromide, m.p. 57-58°C. Further cooling of the filtrate affords 34 g. A 64 g-sample of the phenacyl bromide is added to a stirred mixture containing 212 ml of i-propylamine in 425 ml of ethanol under N_2 atmosphere at 5°C. The temperature rises to 12°C and a clear solution is obtained. The solution is poured into ice (2 L) containing 500 ml of concentrated HCl and 1500 ml of H_2O . After stirring for 20 minutes, the mixture is filtered and the solid is washed with H_2O . On drying this gives 98.64 g, m.p. 200-203°C dec. This solid is dissolved in 400 ml of refluxing methanol, 400 ml of isopropyl alcohol is added, and the solution is concentrated to 400 ml. On cooling and collecting crystals, 54.36 g of ketoamine melting at 213-215° dec is obtained. This material (16 g) is added to 150 ml of methanol which contains 2 g of 5% Pd/carbon and hydrogenated in a Paar vessel at 42 p.s.i.g. of H_2 . The mixture is filtered and the filtrate is evaporated. The residue is mixed with 50 ml of isopropyl alcohol and evaporated to dryness to afford a syrup, which is mixed with 100 ml of ethanol. The crystals are collected, washed with diethyl ether and dried to give 10.77 g, m.p. 129-132°C, of the title compound.

By substituting tert-butylamine for isopropylamine, m -hydroxy- α -[tert-butylamino]methyl]benzyl alcohol hydrochloride, m.p. 150-154°C dec. is obtained. Substitution of isopropylamine with diisopropylamine, benzylamine and allylamine affords m -hydroxy- α -[(diisopropylamino)methyl]-

benzyl alcohol, m-hydroxy- α -[(benzylamino)methyl]benzyl alcohol, and m-hydroxy- α -[(allylamino)methyl]benzyl alcohol hydrochlorides, respectively.

EXAMPLE 13

5. 4-Amino- α [(tert-butylamino)methyl]-3,5-diiodobenzyl Alcohol Hydrochloride

In 10 ml of acetic acid, 0.42 g of p-amino- α -[(tert-butylamino)methyl]benzyl alcohol is stirred under N_2 atmosphere and 0.48g of N,N -dichlorobenzenesulfonamide and 10.0.6g of NaI are stirred under N_2 atmosphere for 20 minutes. After 3 days, the mixture is poured into ice and the mixture is basified with 50% aq. NaOH. This mixture is extracted with CH_2Cl_2 (3 x 25 ml) and chromatographed on a SiO_2 plate using 1% NH_4OH /20% CH_3OH/CH_2Cl_2 to afford 0.22g of the title compound. The reaction is repeated on a larger scale (8X) and the eluted crude product is dissolved in 100 ml of ethanol/10 ml of H_2O , stirred and 10% HCl is added to give pH 3. The mixture is evaporated to dryness in vacuo. Isopropyl alcohol is added and the mixture is evaporated to dryness. This process is repeated twice and the residue is crystallized from methanol/isopropyl alcohol by allowing methanol to evaporate until crystals form (methanol is used to dissolve the crude material before isopropyl alcohol is added). On cooling, 2g of the title compound is obtained melting at 187°C dec.

Anal. Calc'd for $C_{12}H_{19}ClI_2N_2O$: C, 29.02; H, 2.86; N, 5.64.

Found: C, 29.11; H, 3.64; N, 5.64.

EXAMPLE 14

α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl Alcohol Hydrochloride

An alternate procedure for preparing the title compound and the compounds described in Example 9 is exemplified. Thus, 10 g of 4-amino- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is added to 100 ml of 50-52% H_3PO_4 and the mixture is stirred and cooled to 8°C in ice while 2.77 g of $NaNO_2$ in 15 ml of H_2O is added over 65 minutes. Foaming occurs and is controlled with antifoaming silicone.

After 20 minutes, the mixture is stirred 2 hours without cooling. The mixture is then poured into ice-H₂O mixture and 50% aq. NaOH solution is added until the mixture is alkaline. The alkaline mixture is extracted with CH₂Cl₂ three 5 times to give 200 ml of solution, which is washed with 25 ml of 2% NaOH and dried over MgSO₄ and evaporated to dryness in vacuo to give 9.13 g of brown oil. On standing, the oil solidifies, and it is dissolved in 100 ml of ethanol containing 10 ml of H₂O. The solution is acidified to pH 3 with 10 10% HCl and evaporated to dryness. The residue is treated with 50 ml of isopropyl alcohol and evaporated to dryness. This procedure is repeated to afford an off-white solid which is dissolved in methanol. The solution is evaporated in vacuo to afford a syrup, which is diluted with 50 ml of isopropyl alcohol and allowed to stand. The crystals which form are collected, washed with isopropyl alcohol and dried to yield 7.8 g, m.p. 217-221°C dec., of the title compound.

The compound described in Example 6 is similarly prepared. Deamination of 4-amino-3,5-dibromo-a-[(tert-butyl-amino)methyl]benzyl alcohol affords 3,5-dibromo-a-[(tert-butylamino)methyl]benzyl alcohol, m.p. 249-251°C dec.

EXAMPLE 15.

4-Amino-3,5-dichloro-8-methoxyphenethylamine hydrochloride

Under N₂ atmosphere, 11 g of 4-amino-a-[(tert-butyl-amino)methyl]-3,5-dichlorobenzyl chloride is added to 75 ml of methanol at 0°C. After 20 minutes, the cooling bath is removed and the reaction mixture is stirred at ambient temperature. After the reaction is completed, the mixture is evaporated to dryness in vacuo. The residue is stirred in 30 75 ml of H₂O and the mixture is made alkaline with 6N NaOH solution and extracted with CH₂Cl₂ (3 x 50 ml). The organic phases are dried over MgSO₄ and evaporated to dryness to afford an orange oil. This oil is dissolved in 150 ml of absolute EtOH and acidified with HCl/isopropyl alcohol solution to pH 2. The solution is evaporated to dryness and the residue is stirred in 75 ml of ethyl acetate. After cooling, this affords a pale yellow solid which is collected to give

6.97 g of the title compound, m.p. 195-198°C dec.

Similarly, substitution of ethyl alcohol, isopropyl alcohol, n-butyl alcohol and n-hexyl alcohol affords the corresponding β -ethoxy, β -isopropoxy, n-butoxy, and n-hexyl- β -oxy phenethylamine hydrochlorides.

EXAMPLE 16

4-Amino- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl chloride

Under N_2 atmosphere, 27.72 g of 4-amino- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is added to 200 ml of thionyl chloride stirred at 0-5°C. After addition is completed, the reaction mixture is stirred at ambient temperature for 3 hours. Subsequently, the mixture is evaporated to dryness in vacuo to afford 37.34 g of yellow solid, 15 which is used as is.

EXAMPLE 17

Alternate Procedure for 4-Amino-3,5-dichloro- β -methoxy-phenethylamine hydrochloride

I. 100 ml of methanol, 10 g of 4-amino- α -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is stirred in an ice bath and dry HCl gas is introduced into the solution. After saturation of the solution, the mixture is stirred at room temperature for an hour and evaporated to dryness. The solid is then stirred in ethyl acetate to 25 afford the title product, which is collected by filtration.

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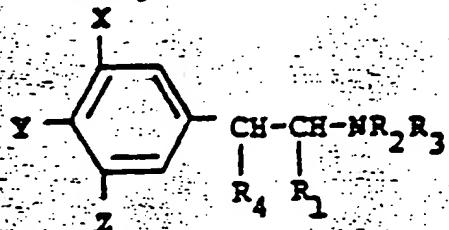
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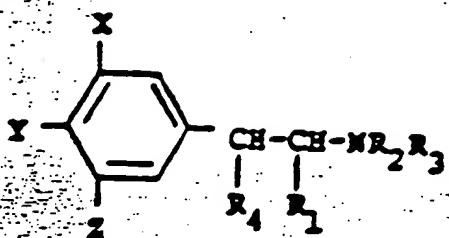
CLAIMS

1. An Animal feed composition comprising a balanced diet and from 0.01 to 400 grams per ton of feed of a compound of the following formula:



wherein X is hydrogen or halogen (fluorine, chlorine, iodine or bromine, but preferably chlorine or bromine); Y is hydrogen, NH_2 or NHCOR_5 ; Z is hydrogen, halogen (fluorine, chlorine, iodine or bromine, but preferably chlorine or bromine) or OH; R_1 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl; R_2 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl (straight or branched-chain) or $\text{C}_3\text{-C}_4$ alkenyl; R_3 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl (straight or branched-chain), $\text{C}_3\text{-C}_6$ -cycloalkyl, methoxypropyl, $\text{C}_3\text{-C}_4$ alkenyl, phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl or benzyl; and when R_2 and R_3 are taken together with the nitrogen to which they are attached, they may represent morpholino or $\text{N}'\text{-C}_1\text{-C}_4$ alkylpiperazino; R_4 is hydrogen, hydroxyl or OR_6 ; R_5 is hydrogen or $\text{C}_1\text{-C}_4$ alkyl; R_6 is $\text{C}_1\text{-C}_6$ alkyl; with the provisos that when R_3 is phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl, cycloalkyl $\text{C}_3\text{-C}_6$, benzyl or methoxypropyl, R_2 is hydrogen; and when Z is OH, X and Y are hydrogen; and when Y is NHCOR_5 , at least one of X and Z is hydrogen; and provided also that at least one of X, Y and Z represents a substituent other than hydrogen; racemic mixtures of the above-identified compounds and the optically active isomers and non-toxic, pharmacologically acceptable acid addition salts thereof.

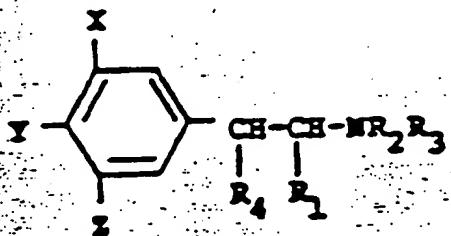
2. A method for the preparation of an animal feed composition comprising admixing an animal feed with from 0.01 to 400 grams per ton of feed of a compound of the following formula:



wherein X, Y, Z, R₁, R₂, R₃ and R₄ are as defined above.

3. A composition according to Claim 1 wherein the compound is 4-amino- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride; 4-amino-3,5-dibromo- α -[(diisopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro- α -[(diisopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dibromo- α -[*(tert*-butylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro- α -[(methylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro- α -[(isopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro- α -[(allylamino)-methyl]benzyl alcohol; α -[4-amino-3,5-dichlorophenyl]-4-morpholineethanol hydrochloride and 4-amino-3-bromo- α -[*(tert*-butylamino)methyl]-5-chlorobenzyl alcohol hydrochloride; α -[*(tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride.

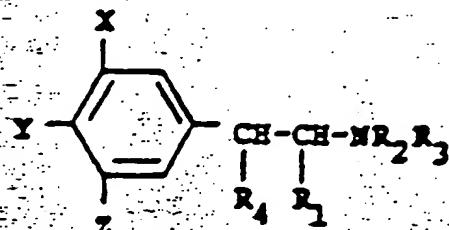
4. An animal feed supplement useful for enhancing the growth rate and for reducing the fat deposition in warm-blooded animals comprising from about 75% to 95% by weight of a compound of the following formula:



wherein X, Y, Z, R₁, R₂, R₃ and R₄ are as defined in Claim 1, above, and from about 5% to 25% by weight of a suitable carrier or diluent.

5. An injectable composition useful for enhancing the growth rate and for reducing the fat deposition in warm-

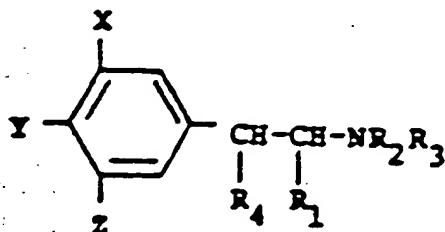
blooded animals comprising as an active ingredient a compound of the following formula:



wherein X, Y, Z, R₁, R₂, R₃ and R₄ are as defined in Claim 1, above, and a pharmaceutically acceptable carrier.

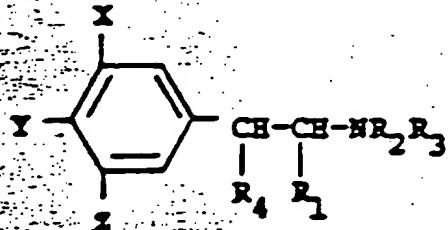
6. A composition according to Claim 5 wherein the active ingredient is present in an amount of from 0.001 to 50 mg/kg. of body weight.

7. An implant useful for enhancing the growth rate and reducing the fat deposition of meat-producing animals comprising as an active ingredient a compound of the following formula:



wherein X, Y, Z, R₁, R₂, R₃, and R₄ are as defined in Claim 1, above, and a pharmaceutically acceptable carrier.

8. A compound of formula:



wherein X is halogen;

Y is hydrogen or NH₂;

Z is halogen;

R₁ is hydrogen or C₁-C₄ alkyl;

R₂ is hydrogen, C₁-C₄ alkyl or C₃-C₄ alkenyl;

R₃ is hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, methoxypropyl, C₃-C₄ alkenyl, phenyl, 2-hydroxyethyl, a,a-dimethylphenethyl or benzyl; and when R₂ and R₃ are taken together with the

nitrogen to which they are attached, they may represent morpholino or N'-C₁-C₄ alkyl-piperazino; R₄ is hydroxy or OR₆; R₆ is C₁-C₆ alkyl; with the provisos that when Y is NH₂, then R₄ is OR₆; and when Y is hydrogen, R₂ is hydrogen; racemic mixtures of the above-identified compounds and the optically active isomers and non-toxic, pharmacologically acceptable acid addition salts thereof.

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION SEE Cl 9
Category	Category of document(s) for disclosure, where appropriate, of relevant passages	Reference to claim(s)	
D	US - A - 3 536 712 (J. KECK et al.) * Claim 1; column 32, lines 14-25; examples 202-205 *	1,4-7	A 23 K 1/16 C 07 C 91/18 91/40 93/14
X	ARZNEIMITTEL FORSCHUNG, (Drug Res.) vol. 26, no. 7a, July 1976, pages 1420-1427 Aulendorf, DE. H. UEBERBERG et al.: "Tierexperimentelle Untersuchungen zur Verträglichkeit von NAB 365 (Clenbuterol)" * Summary; page 1423, section 3.1.2; page 1425, section 3.2.2 *	1-7	TECHNICAL FIELDS SEARCHED SEE Cl 9
X	NL - A - 246 478 (RADOUCO-THOMAS S.M-A) * Claims 1,12,15-17,19; page 4, lines 2-30; page 5, lines 1-7 *	1-7	A 23 K 1/16 C 07 C 91/18 91/40 93/14 A 61 K 31/135 31/165
	US - A - 3 818 101 (C.A. BAILE et al.) * Abstract; columns 1,2; column 7, lines 55-68; column 8, lines 1-68 *	1-7	CATEGORY OF CITED DOCUMENTS
X	GB - A - 1 141 606 (SOCIETE D'ETUDES DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ET MEDICALES) * Claim 1 *	8	<ul style="list-style-type: none"> I: pertinency reference A: technological background C: non-pertinency disclosure P: non-pertinency disclosure T: theory or principle underlying the disclosure E: conflicting application D: document cited in the application L: document for other purposes R: reference of the cited document S: supplementary document
X	The present search report has been drawn up for all claims		
Date of completion of the search		20-11-1980	GALLIGANI
The Hague			



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DOCUMENTS CONSIDERED TO BE RELEVANT		CLASSIFICATION OF THE APPLICATION AS CLAIMED
Citation of document via number, name of inventor or assignee		
X	DE - A - 1 902 603 (C.H. BOEMIGER & SOHN) • Claim 1; page 5, paragraph 4 • ----	
X	GB - A - 1 218 135 (ABBOTT LABORATORIES) • Claim 1 • ----	8
TECHNICAL FIELDS SEARCHED (see Cl 7)		
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